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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/683,549	10/10/2003	Fabian Somers	DI-5954 (BXTD 9004.6)	2624

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SENNIGER POWERS
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS, MO 63102

EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 01/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/683,549	SOMERS ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18,20-22,24-31,33-35 and 37-40* is/are pending in the application.

4a) Of the above claim(s) *18 and 38-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,20-22,24-31,33-35 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Applicant's election without traverse of the species erythropoietin plus Gly-His in the reply filed on February 4, 2005 is acknowledged.

Claims 18 and 38-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 4, 2005.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 16, 21, 22, 24-26, 30, 31, 33, 34, and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Sato et al (U.S. Patent Application Publication 2003/0092622). Sato et al teach stabilized pharmaceutical compositions comprising a protein such as erythropoietin which is produced recombinantly in BHK or CHO cells and a stabilizer which is Trp or a derivative thereof in a concentration of 0.1-300 mM, preferably 1-10 mM. The EPO concentrations can range preferably from 750 to 72,000 IU/ml. The derivatives can be dipeptides such as Cbz-Gly-Trp, Cbz-Gly-Trp-OMe, Cbz-Gly-Gly-Trp-OMe, Gly-Trp, Ala-Trp, etc. The compositions are substantially free of protein stabilizers such as human serum albumin, and in the examples directed to EPO compositions, are free of protein stabilizers such as human serum albumin. The compositions can comprise a surfactant such as polysorbate 20 or 80. Surfactant concentrations are preferably 0.005-3% (w/v). The solutions are intended to be administered parenterally. See, e.g., paragraphs [0042], [0043], [0046]-[0048], [0056], [0057], and [0060]. For the dipeptide and tripeptide stabilizers mentioned above, plus others, see especially paragraph [0047], lines 21-38, 40, and 41. With respect to instant claim 34, the Trp derivatives of Sato et al are deemed to constitute "derivatives" of the specific peptide stabilizers claimed by Applicants, because of their

similarity in structure (i.e. dipeptides or tripeptides having at least one amino acid in common) and structure (i.e. ability to stabilize protein compositions). Sato et al do not teach or specifically exemplify an erythropoietin composition comprising one of the dipeptide or tripeptide stabilizers, with the composition being free (as opposed to substantially free) of serum albumin. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the dipeptide and tripeptide stabilizers taught by Sato et al to stabilize the erythropoietin compositions taught by Sato et al because it is desirable to stabilize erythropoietin compositions and because the dipeptide and tripeptide stabilizers taught by Sato et al would have been expected to exhibit stabilizing properties useful for the erythropoietin compositions taught by Sato et al. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to formulate the dipeptide- and tripeptide-stabilized erythropoietin compositions suggested by Sato et al so that they are free (as opposed to substantially free) of serum albumin, because it would have been prima facie obvious to omit a component which Sato et al prefer not to be present, and because it is preferable in the pharmaceutical arts to minimize the number of components in a pharmaceutical composition so as to minimize the chances of adverse side effects.

4. Claims 24-29 and 35 are rejected under 35 U.S.C. 103(a) as being obvious over Sato et al (U.S. Patent Application Publication 2003/0092622) as applied against claims 16, 21, 22, 24-26, 30, 31, 33, 34, and 37 above, and further in view of the WO Patent Application 02/14356. Sato et al are not limited to stabilizing any particular type of erythropoietin, but do not teach stabilizing an erythropoietin which is erythropoietin omega. The WO Patent Application '356 teaches erythropoietin omega to be a form of erythropoietin which is useful in treating fatigue,

pain, chronic heart failure, dysrythmia and dementia. See, e.g., the Abstract; page 4, line 24 - page 9, line 14; and claim 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to stabilize the erythropoietin omega of the WO Patent Application '356 using the stabilizing agents of Sato et al because it would be desirable to stabilize the erythropoietin omega of the WO Patent Application '356 so as to preserve its therapeutic activities, and because the stabilizing agents of Sato et al have been used to preserve very closely related erythropoietin analogs and therefore would have been expected to be useful in stabilizing erythropoietin omega.

5. Claims 16, 21, 22, 24-26, 30, 31, 33, 34, and 37 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 01/64241. The WO Patent Application '241 is equivalent to Sato et al (U.S. Patent Application Publication 2003/0092622) applied above, but is available as prior art against Applicants' claims under 35 U.S.C. 102(b). The WO Patent Application '241 suggests Applicants' claims for the same reasons that Sato et al suggest Applicants' claims.

6. Claims 24-29, and 35 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 01/64241 as applied against claims 16, 21, 22, 24-26, 30, 31, 33, 34, and 37 above, and further in view of the WO Patent Application 02/14356. The WO Patent Application '241 in view of the WO Patent Application '356 suggests Applicants' claims for the same reasons that Sato et al in view of the WO Patent Application '356 suggest Applicants' claims.

7. Claims 16, 20-22, 24, and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Cormier et al (U.S. Patent Application Publication 2002/0058608). Cormier et al disclose an aqueous composition comprising a drug which is preferably a protein or a polypeptide and a

buffer which is preferably Gly-His, at least partly in salt form. The drug can be erythropoietin. The buffer is present in a concentration of 10 mM to 1 M (2.1-212 g/L), preferably 25-250 mM (5.3-53 g/L). No serum albumin is present in the composition. See, e.g., paragraphs [0034], [0041], [0047] and claims 1, 6, and 8. Cormier et al do not specifically teach a composition comprising both erythropoietin and Gly-His, and do not teach the buffer concentration of instant claim 22. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer erythropoietin using the Gly-His buffer of Cormier et al because Cormier et al disclose that erythropoietin is a protein which can usefully be administered in their formulations, and because Gly-His is a preferred buffer for Cormier et al's compositions. With respect to the limitation "recombinant" in instant claim 24, process of making limitations do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal buffer concentrations embraced by the disclosure of Cormier et al because concentration is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts. With respect to the limitation "for administration by parenteral injection" in instant claim 37, an intended use limitation does not impart patentability to product claims where the prior art products are capable of the claimed intended use even though the prior art does not intend to use the prior art products in Applicants' intended manner. See MPEP 2111.02(II). The aqueous solutions suggested by Cormier et al are capable of being administered by parenteral injection, and therefore Applicants' intended use limitation does not distinguish over Cormier et al.

8. Claims 24-29 are rejected under 35 U.S.C. 103(a) as being obvious over Cormier et al (U.S. Patent Application Publication 2002/0058608) as applied against claims 16, 20-22, 24, and 37 above, and further in view of the WO Patent Application 02/14356. Cormier et al are not limited to stabilizing any particular type of erythropoietin, but do not teach stabilizing an erythropoietin which is erythropoietin omega. The WO Patent Application '356 teaches erythropoietin omega to be a form of erythropoietin which is useful in treating fatigue, pain, chronic heart failure, dysrythmia and dementia. See, e.g., the Abstract; page 4, line 24 - page 9, line 14; and claim 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to formulate the erythropoietin omega of the WO Patent Application '356 in the compositions of Cormier et al because it would be desirable to administer the erythropoietin omega of the WO Patent Application '356 iontophoretically, and because the compositions of Cormier et al have been used to administer a wide range of proteins and therefore would have been expected to be useful in administering erythropoietin omega. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal concentrations for the erythropoietin omega to be administered in the compositions of Cormier et al as modified above by the WO Patent Application '356 because concentration is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts.

9. Claims 30, 31, 33, and 34 are rejected under 35 U.S.C. 103(a) as being obvious over Cormier et al (U.S. Patent Application Publication 2002/0058608) as applied against claims 16, 20-22, 24, and 37 above, and further in view of Holladay et al (U.S. Patent No. 6,328,728). The compositions of Cormier et al are to be administered by transdermal electrotransport, i.e.

iontophoretically (see, e.g., the Abstract, paragraph [0003], and claim 1), but Cormier et al do not teach the presence of a surface active agent in the composition comprising the protein or polypeptide. Holladay et al et al teach including a surfactant such as a polyoxyalkylene sorbitan fatty acid ester in a composition comprising a protein or polypeptide which is to be electrotransported across a body surface, i.e. across the skin. The surfactants have the benefit of increasing the flux of the protein or polypeptide across the body surface and of decreasing the biodegradation of the proteins or polypeptides. See, e.g., column 3, line 55 - column 4, line 6, and claims 4 and 8. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to include a surfactant such as a polyoxyalkylene sorbitan fatty acid ester of Holladay et al in the compositions of Cormier et al so as to increase the flux and to decrease of biodegradation of the erythropoietin to be administered by Cormier et al. Note that motivation to combine under 35 U.S.C. 103 need not be the same as Applicants' expressed motivation. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal concentrations for the surfactants in the compositions of Cormier et al as modified above by Holladay et al because concentration is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts.

10. Claim 35 is rejected under 35 U.S.C. 103(a) as being obvious over Cormier et al (U.S. Patent Application Publication 2002/0058608) in view of the WO Patent Application 02/14356 as applied against claims 24-29 above, and further in view of Holladay et al (U.S. Patent No. 6,328,728). The compositions of Cormier et al as modified above by the WO Patent Application '356 are to be administered by transdermal electrotransport, i.e. iontophoretically (see, e.g., the

Abstract, paragraph [0003], and claim 1), but Cormier et al do not teach the presence of a surface active agent in the composition comprising the protein or polypeptide. Holladay et al et al teach including a surfactant such as a polyoxyalkylene sorbitan fatty acid ester in a composition comprising a protein or polypeptide which is to be electrotransported across a body surface, i.e. across the skin. The surfactants have the benefit of increasing the flux of the protein or polypeptide across the body surface and of decreasing the biodegradation of the proteins or polypeptides. See, e.g., column 3, line 55 - column 4, line 6, and claims 4 and 8. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to include a surfactant such as a polyoxyalkylene sorbitan fatty acid ester of Holladay et al in the compositions of Cormier et al as modified above by the WO Patent Application '356 so as to increase the flux and to decrease of biodegradation of the erythropoietin omega to be administered. Note that motivation to combine under 35 U.S.C. 103 need not be the same as Applicants' expressed motivation. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal concentrations for the surfactants in the compositions of Cormier et al as modified above by the WO Patent Application '356 and Holladay et al because concentration is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts.

11. Applicant's arguments filed November 22, 2005 have been fully considered but they are not persuasive.

The claims remain rejected over Sato et al (U.S. Patent Application Publication 2003/0092622) and over the WO Patent Application 01/64241 to the extent that Applicants' claims recite that the peptide stabilizer can be "derivatives thereof" in general. As noted by

Applicants, the examiner maintains that the Trp-based stabilizers of the two references constitute "derivatives" as claimed by Applicants in view of the similarity in structure and function between the Trp-based stabilizers and Applicants' specific dipeptide stabilizers. Applicants' specification does not contain any definition of "derivatives", and during prosecution claim terminology is given its broadest reasonable interpretation consistent with the specification. See MPEP 2111. Hayward et al (U.S. Patent Application Publication 2005/0288222 - see paragraph [0048]); Bajaj (U.S. Patent No. 6,624,289 - see column 6, lines 24-27); and Pierson, III et al (U.S. Patent No. 6,538,028 - see column 11, lines 12-16); show that "derivative" is interpreted broadly in the art, and that peptide derivatives do not have to have the same number of amino acids and do not even have to be peptides in order to constitute derivatives of a given peptide. The examiner agrees that the peptide stabilizers of the two references are different peptides than the specific dipeptide stabilizers recited in the rejected claims. However, this is the reason why Applicants include "derivatives thereof" in their claims, i.e. in order to encompass peptide stabilizers which are different than those specifically recited.

With respect to the obviousness rejections based upon Sato et al (U.S. Patent Application Publication 2003/0092622) or the WO Patent Application 01/64241, each in view of the WO Patent Application 02/14356, Applicants additionally note that the WO Patent Application '356 does not mention that erythropoietin alpha can be formulated using peptide stabilizers, and that therefore there is no motivation to combine the WO Patent Application '356 with either Sato et al or the WO Patent Application '241. The examiner does not agree. Motivation for combination of the references is supplied by Sato et al and by the WO Patent Application '241, which suggest that erythropoietin in general can be stabilized with the disclosed stabilizers. The

specific erythropoietin of the WO Patent Application '356 is of the type which Sato et al and the WO Patent Application '241 suggest can be stabilized. Motivation necessary to establish prima facie obviousness need not be found in any particular reference, but can be found upon a consideration of the prior art as a whole.

Applicants' statement of "the present invention" at page 8, last line, through page 9, line 3, of the response does not accurately describe the presently claimed invention. As discussed above, Applicants' presently claimed peptide stabilizers are not limited to the specific di- and tri-peptides recited at page 9, lines 1-2, of the response, but also include "derivatives thereof". See claims 16, 34, and 37, line 4 of each claim.

The obviousness rejections based upon Cormier et al (U.S. Patent Application Publication 2002/0058608) as the primary reference are maintained. Cormier et al prefer Gly-His as a dipeptide stabilizer (see, e.g., Examples 1-4 and claim 6), prefer polypeptides or proteins as their drug (see, e.g., claim 8), and specifically list erythropoietin as a polypeptide or protein which can be formulated according to their invention (see page 4, column 1, line 3). These preferences in Cormier et al are deemed to provide sufficient motivation to chose the combination of Gly-His and erythropoietin. With respect to Cormier et al and serum albumin, the examiner assumes that a component which is not mentioned as being present in a composition, and which would not have been expected to be present in the composition, is not present in the composition. Whether the basis for this assumption is inherency or some other reason is not seen to be relevant. The alternative is that a given prior art composition could be re-patented an infinite number of times, each patent specifying that the prior art composition does not comprise some component that would never have been expected to be present yet is not

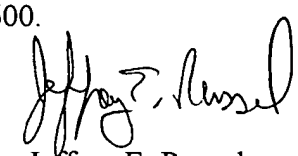
expressly disclosed as being absent. Such a result would be contrary to established patent law. With respect to the combination of Cormier et al with Holladay et al (U.S. Patent No. 6,328,728), Holladay et al prefer the use of polyoxyalkylene sorbitan fatty acid esters as surfactants (see, e.g., Examples 1 and 3, and claim 8), and this provides motivation to select polyoxyalkylene sorbitan fatty acid esters from the surfactants taught by Holladay et al.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

January 3, 2006